Page 2, line 19, please rewrite as follows:

a4

BRIEF SUMMARY OF THE INVENTION

Page 6, line 4, please rewrite the paragraph as follows:

BRIEF DESCRIPTION OF THE DRAWINGS

a5

Reference is directed to the accompanying drawings in which each of Figures 1 to 6 is a series of diagrams illustrating a method according to the invention.

Page 6, line 24, please rewrite as follows:

a6

DETAILED DESCRIPTION OF THE INVENTION

Page 13, line 2, please rewrite the paragraph as follows:

a7

The M13 sequencing primer - 5'-GTAAAACGACGGCCAGT-3' - (SEQ ID No. 1) attached to aminated polypropylene through its 5' end was synthesised as described. A solution of M13 DNA (single-strand, replicative form, 0.1 µl, 200 ng/µl) was applied in two small spots to the surface of the derivatised polypropylene. A solution containing three non-radioactive deoxyribonucleotide triphosphates, dATP, dGTP, TTP (10µmol each), α^{32}P-dCTP (10 µCi), Taq DNA polymerase and appropriate salts, was applied over a large area of the polypropylene, including the area where the M13 DNA had been spotted. The polypropylene as incubated at 37°C for 1 hr in a vapour saturated chamber. It was then washed in 1% SDS at 100°C for one minute, and exposed to a storage phosphor screen for one minute and scanned in a phosphorimager. The regions where the DNA had been applied showed a high level of radioactivity, against a low background where no DNA had been applied. This experiment shows that oligonucleotides tethered to a solid support can act as primers for DNA-dependent synthesis by DNA polymerase, as required for applications using this enzyme for mutation detection.

Page 15, line 27 to page 16, line 29, please rewrite as follows:

An array of VNTRs was made as described in Fig. 4b, in which the anchor sequence was 5'-tgtagtggtgtgatcaaggc-3' (SEQ ID No. 2). The repeat unit was 5'-cttt-3'; stripes, ca 3 mm wide, of sequence variants of the form: Anchor-Repeat$_N$, with N = 4-10, were made as stripes on the surface of a sheet of polypropylene. The synthesis was carried out using 3'-deoxyribophosphoramidites, this chemical orientation produces oligonucleotides tethered through their 3' ends to the polypropylene, and a free 5' hydroxyl group. To create a substrate for ligation, this OH group was phosphorylated by immersing a strip of the polypropylene (3mm x18mm), carrying the array of oligonucleotides, in 0.5 ml of a solution containing 4mM ATP and 77.6 units of polynucleotide kinase with buffer and Mg^{++} according to the supplier's instructions. The reaction was left for 6 hours at 37°C; the strip was removed and immersed in boiling water to kill the polynucleotide kinase. The target sequences, which are complementary to elements of the array oligonucleotides and to the ligation tag, 5'-Anchor-Repeat$_{10}$-Tag and 5'-Anchor-Repeat$_5$-Tag were added to 0.5 ml of a solution, preheated to 95°C containing the tag, 5'-gtggtcactaaagtttctgct-3' (SEQ ID No. 3), which had been labelled at its 5' end using polynucleotide kinase and ^{33}P-gamma-ATP, thermal ligase (500 units), and buffer and salts according to the supplier's instructions. The polypropylene strip was immersed in the hot solution, which was then allowed to cool to 68°C, and left at this temperature for 16 hours. The polypropylene strip was removed and placed in 25% formamide at 95°C for 5 minutes, rinsed in water at the same temperature, dried and exposed to a storage phosphor screen, from which an image of the radioactivity was collected. The results showed counts close to background over most of the array; counts on Anchor-Repeat$_5$ and Anchor-Repeat$_{10}$ were more than five times those over adjacent cells in the array. This experiment indicates that the ligase is able to distinguish length variants of the repeat sequence and gives optimum ligation only when the number of repeats in the target matches that in the allele specific oligonucleotide in the array. Thus, it should easily be possible to detect the two allelic variants in a heterozygote.

Page 17, line 10, please rewrite the paragraph as follows:

An array of VNTR's was made as described in Figure 4B, with the oligonucleotides anchored through their 5' ends. The repeat unit was 5' ttca and the anchoring sequence 5' cttatttccctca (SEQ ID No. 4). Stripes 6mm wide of sequence variants of the form: Anchor-$Repeat_N$ where N= 4-8 were made on the surface of a sheet of polypropylene using "reverse" phosphoramidite monomers.

Page 17, line 18, please rewrite as follows:

A strip of the array (30mm x 2mm) was immersed in a solution of 600pmols of the target oligonucleotide 5'cacagactccatgg$(tgaa)_6$tgagggaaataag (SEQ ID No. 5), 1.4 pmol of oligo 5'ccatggagtctgtg (SEQ ID No. 6) (labelled at its 5' end using polynucleotide kinase and ^{33}P gamma ATP) and buffer and salts according to the suppliers instructions, the total volume being 293 µl. The solution was heated to 65°C and 7 µl of Tth DNA ligase added. The reaction was then cooled to 37°C and left at that temperature for 18 hrs. After removal from the reaction solution the strip was washed in T.E. buffer, blotted dry and exposed to a storage phosphor screen from which an image of the radioactivity was taken. The results showed that the target sequence ligated to the correct sequence with a higher yield than to the shorter and longer sequences in adjacent cells of the array.

Page 19, line 29 to page 20, line 8, please rewrite as follows:

In an experiment similar to the one described in Example 1, an array was created using the human fes/fps locus sequence as a target. The anchor sequence 5'agagatgtagtctcattctttcgccaggctgg 3' (SEQ ID No. 7) was the actual flanking sequence to the attt repeats of the fes/fps microsatellite (EMBL Accession No X06292 M14209 M14589) as it occurs in human genomic DNA. Using a target oligonucleotide representing the 10 repeat allele and ligating a ^{33}P labelled 5' flanking sequence (5' g gag aca agg ata gca gtt c3') (SEQ ID No. 8) and doing a similar experiment to that described above, the resulting radioactivity on the anchor-$repeat_{10}$ cell was over 10 fold that on adjacent cells in the array.

Page 20, line 13 to page 21, line 5, please rewrite as follows:

A primer oligodeoxynucleotide - 5' PO_4 gta aaa cga cgg cca gt 3' (SEQ ID No. 9), attached to aminated polypropylene through its 3' end, was synthesised and phosphorylated as described. A small square (2mm x 2mm) piece of this material was placed in standard ligation buffer, with template oligonucleotide 5'tcg ttt tac cgt cat gcg tcc tct ctc 3' (SEQ ID No. 10) (250 nM) and a protected ligator oligonucleotide 5' NB PO_4 cgc atg acg 3' (250 nM) and ^{33}P labelled extender oligonucleotide 5' gag aga gga 3', where NB is a protecting group based on a photocleavable o-nitrobenzyl derivative. The NB protected phosphate of the ligator oligonucleotide had previously been shown to be unable to take part in the ligation reaction. The NB group had also been shown to be removable by uv light to leave a fully functional phosphate group. To this mixture was added thermus thermophilus DNA ligase (Advanced Biotechnologies) 25u and the reaction incubated at room temperature for 6 hours. The mixture was then irradiated with uv light (20 minutes room temperature) and incubated for a further 12 hours. The polypropylene patch was then washed with 30% formamide at 95°C for 5 minutes, and exposed to a storage phosphor screen for 24 hours and scanned in a phosphorimager. The patch showed a level of radioactivity 50 fold higher than a patch treated in a similar fashion but without addition of the central "ligator" oligonucleotide. In a similar experiment using a phosphorylated ligator oligonucleotide a similar amount of radioactive extender oligonucleotide became covalently attached to a third polypropylene/oligonucleotide primer square.

Page 21, line 11, please rewrite the paragraph as follows:

Four tethered ASOs 5' (gca or t)ag aga gga 3', differing only at their 5' base, were synthesised as described above, with the 3' end attached to aminated polypropylene. Phosphorylation was carried out as described and four squares of polypropylene carrying each ASO were placed in standard ligation buffer along with complementary target oligonucleotide 5' tcc tct ctc cgt cat gcg tat cgt tca at 3' (SEQ ID No. 11) (250 nM). After addition of ^{33}P labelled ligator oligonucleotide 5' cgc atg acg 3' (10 nM) and thermus thermophilus DNA ligase (100u), the mixture was incubated at 37°C for 18 hours. The ASO which was fully complementary to the

target oligonucleotide was found to have acquired 100-fold greater radioactivity through ligation of the labelled ligator than the non-complementary ASOs.

Page 21, line 29 to page 22, line 15, please rewrite as follows:

Template oligonucleotide 5' tcc tct ctc cgt cat gcg tat cgt tca at 3' (SEQ ID No. 12) (250 nM), phosphorylated, ^{33}P labelled, extender oligonucleotide 5' PO_4gag aga gga 3' (10 nM) and ligator sequence 5' gca gta cg 3' (250 nM) were mixed together in standard ligation buffer with DNA ligase 25 u. This mixture was incubated at 35°C. Samples of this mixture were removed and the reaction stopped by addition of formamide at 15, 30, 60, 120 and 240 minutes. The ligated and unligated products were separated by 20% denaturing polyacrylamide gel electrophoresis. The gel was exposed to a phosphor screen for 18 hours and scanned by a phosphorimager. The relative proportions of ligated to unligated products of the reaction were then measured. 50% of the extender sequence had been ligated to the ligator sequence in 30 minutes. By comparison in a similar experiment with ligator 5' gca tga ag 3' after 30 minutes only 1% of the extender sequence had become ligated.

IN THE CLAIMS

Cancel without prejudice claims 1-11.

IN THE SEQUENCE LISTING

Please transfer the paper and computer-readable copies of the Sequence Listing from the parent application Serial No. 09/502,778 filed February 11, 2000. The Sequence Listing of the present application is identical to the parent application, and the paper and computer-readable copies of the Sequence Listing in the parent application are identical to each other. No new matter was added to the Sequence Listing in the parent application, and thus, no new matter is added to the Sequence Listing of the present application.